DR. ZIVIN: Okay. Now, I would like to know what criteria you would have for failure of surgery.

DR. FUTRELL: The issues of failure of surgery are not going to happen--it doesn't come up very often because we haven't done surgery on a lot of these patients. But when I went back to Utah in '97 and the PFO issue was kind of coming of age, I sent a total of about ten patients to surgery.

One of those patients had a failure of surgical closure and had to be reoperated. Now, the failure of surgical closure in that particular case was defined that she was out in her yard--said that she was working in her yard, felt a pop, and all of her symptoms that went away when her PFO had surgically--post come back.

DR. ZIVIN: With due respect, I would prefer not to discuss anecdotes. I would prefer to discuss data.

DR. FUTRELL: So the data was that she was put on the TC--

DR. ZIVIN: That was one patient. I would prefer to--

DR. FUTRELL: It is the only surgical failure I have had, Justin. It is the only one.

Out of ten patients, I have one failure.

DR. ZIVIN: So, obviously, you don't have statistical data to prove that your therapy is better, worse or the same as doing nothing.

DR. FUTRELL: We know that patients are going to surgical closure for PFOs. We know what the complications of heart surgery are. We know about the cognitive complications. We know about the expense. We know that patients with PFOs are having failures with medical therapy and those patients are either going to go to surgical closure or to catheter closure.

DR. ZIVIN: Do we know that patients who are having PFOs are having complications?

DR. FUTRELL: Of surgery?

DR. ZIVIN: Yes.

DR. FUTRELL: We haven't done the same degree of neuropsychological testing for the PFO indication. Those are pump studies, general pump studies.

DR. ZIVIN: You had in your data something like 25 percent of patients had complications due to surgery.

DR. JENKINS: I'm sorry?

DR. ZIVIN: In your data, you proposed --

DR. JENKINS: These patients did have surgery.

DR. ZIVIN: At various different levels as 25 up to 80 percent of the patients had complications as a consequence of surgery.

DR. JENKINS: I'm sorry? None of the patients presented to you had surgery. None.

DR. ZIVIN: Then who got the closures?

DR. JENKINS: I'm sorry? This is a percutaneous--

DR. ZIVIN: What I am saying is approximately 25 percent, in some cases up to 80 percent, had complications as a consequence of device placement.

DR. TRACY: Can I just clarify? I think he is asking you about the patients that you had, trying to make a comparison between what would have happened in a surgical group versus what happened with your percutaneous closure device and he is reporting what he believes is your complication rate from the percutaneous.

Am I getting that correct? So a comparison between percutaneous closure complication versus surgical closure complication.

DR. JENKINS: I think that seven of the

patients in the pivotal cohort, or 14 percent, met the safety definition for the study of having had a moderately serious or a serious even attributable by the safety committee to the device or the implant procedure or to the catheterization, itself.

So I am unclear as to where the figure of 25 to 80 percent is from.

DR. ZIVIN: If you look through your data, you will find it. But, what fraction of age-matched patients had complications as a result of medical therapy?

DR. JENKINS: I'm sorry?

DR. ZIVIN: What percentage of patients age-matched had complications of medical therapy during that same time period.

DR. JENKINS: Age-matched?

DR. ZIVIN: Yes.

DR. JENKINS: I am not following. You mean you would like to see the failures of medical therapy stratified by age?

DR. ZIVIN: No; I want complications of the therapy, not failures of the therapy, because then we will get, under the next question, what fraction of your patients would, over a long period

of time, have strokes. You followed them for six months.

DR. JENKINS: We followed the pivotal cohort for median of 6.5 months.

DR. ZIVIN: Okay.

DR. JENKINS: Your question is?

DR. ZIVIN: I want to know what fraction of the patients were injured by therapy, by your device placement, and what fraction of the patients were injured by medical therapy during that same period of time. You told me what the incidence of strokes was in treated patients with medical therapy. I want to know what the comparable patient size population of device-placed therapy would also have as complications over a comparable period of time.

DR. JENKINS: Could we go back to the slide of the patients, the actual complications that occurred? I think that would be the easiest, the primary safety outcomes slide from my presentation which lists all of the complications.

DR. ZIVIN: I was asking for efficacy, not safety.

DR. JENKINS: You are defining complication as part of efficacy? I'm sorry; we

didn't collate the data with complications defined as part of efficacy.

DR. ZIVIN: Okay. So you have evidence of safety but not efficacy. All medical devices are required to prove now both a balance between safety and efficacy. You are applying for a standard that requires evidence of safety which you are not clear about and efficacy which you have no data about whatever; is that correct?

DR. JENKINS: I would not agree with that statement; no.

DR. ZIVIN: Tell you how you would agree with it.

DR. JENKINS: I think that we did show you efficacy data.

DR. ZIVIN: Please show it to me.

DR. JENKINS: Could we go back and show those slides to the primary efficacy outcome data slide.

[Slide.]

These are efficacy data using closure status as the measure of efficacy.

DR. ZIVIN: I want to measure it as a function of stroke rates.

DR. JENKINS: Then go forward to the

secondary efficacy outcome data.

[Slide.]

These are efficacy outcome assessments of strokes. These are difficult to benchmark in a study without a comparison cohort. Therefore, we provided the expected stroke rates as shown on the following slides.

DR. ZIVIN: Why wasn't a comparison group chosen as a comparison group? For example, it is unethical to withhold a form a therapy either anticoagulation or aspirin from such patients.

DR. JENKINS: I'm sorry; I'm not following.

DR. ZIVIN: All of those patients should have been, according to current guidelines, either been on aspirin or anticoagulation.

DR. JENKINS: Right.

DR. ZIVIN: You said you didn't have a comparison group. Where are they?

DR. JENKINS: If you show, actually, a slide that we showed earlier--

[Slide.]

--we do show the medications that the patients were on at the entry to the study. The vast majority of patients were being treated with

medical therapy by their physicians at the time of entry to the study.

DR. ZIVIN: And then you did not, then, continue on with another arm of the study to show a parallel comparison between the patients who remained on the medical therapy versus your device.

DR. JENKINS: If I could just make a comment. I think it is pretty clear from the data that has been presented that we have been clear that there was no comparison arm.

DR. ZIVIN: I understand that.

DR. JENKINS: So you seem to be asking why we didn't do that.

DR. ZIVIN: That's right.

DR. JENKINS: It is a study that was designed as a single-arm trial with a judgment-based entry criteria and a structured follow up overseen by a safety committee and a core lab from its inception.

DR. ZIVIN: Your trial represents a history of clinical-trial development not the future. What you were proving was that your device closed a lesion safely, or at least moderately safely. You did not show that your therapy was better than best medical therapy for this

condition. Under those circumstances, I see no indication for believing that you have proven that the device is useful for anything.

DR. JENKINS: Just to point out, less than one year ago, this similar type of data was used by this panel to grant a PMA approval for VSD.

DR. ZIVIN: The fact is that the PMA approval may have been on a different standard than we are trying to achieve today.

DR. TRACY: I think we need clarification on what is required from the FDA for approval of a device.

DR. ZUCKERMAN: Right. First of all, a reference was made to the PMA approval one year ago.

At that time, a similar type device was being brought before this panel for a different indication. It is very important to stress that; a different indication. The standard of evidence, however, remains the same. It is a relative assurance of safety and efficacy.

Of course, we always read those definitions into our record at the end of this panel meeting, but it is important to note that efficacy is also required for PMA approval as

opposed to what is required for HDE approval.

DR. TRACY: Anything else?

DR. MARLER: Can I follow up? The reason I was talking about the indications for proposed use is I was trying to follow your set of logic. I think your argument for effectiveness, essentially your primary outcome was it plugged the hole up and it did so very well.

The reason I am--and then the logic is that the stroke that is presumably caused by something going through that hole is prevented because the hole is plugged up. It is pretty obvious and intuitive. But the problem is that when I look at the literature about PFO it is not really clearly documented what the association between PFO and stroke is.

Is it related to other factors? Is it an entirely independent risk factor? In some cases, it seems to be. However, I guess we are going to have to disagree about your indications for proposed use but it seems to me a large number of the patients who entered WARSS and were found to have PFOs after having an original stroke, would have been eligible.

Yet, in that case, the incidence of stroke

was similar in patients with PFO and without. So, it seems to me that there isn't that much evidence that just the presence of the PFO, itself, is the entire source of the risk of the stroke.

To me, that argues more strongly that you do need some kind of control group in which you prospectively define exactly the subset that you talk about when we are trying to get the indications defined, and compare the two groups with or without closure.

Do you have any--how do you address that?

DR. FUTRELL: Actually, I think we probably agree on more things than we disagree. Let me see if I can explain it in a way that illustrates that.

First of all, just a point of clarification. I was not involved in this trial of the patients who were presented today. I have been sort of an innocent bystander who has been taking care of patients in clinic and has found patients with presumed paradoxical emboli who were failing medical therapy.

My option has been to send these people to surgery. I have been waiting, just hoping the catheter devices would be safe to place and would

close the PFO. So I have looked at the study from that perspective, to say are these PFOs closed and how did these patients do as far as outcomes.

Then this has been followed up with my own experience with the center, with our interventional cardiologist, Sharon Sorenson, who has placed about forty or fifty of these devices, some of which have been in my patients. So that is the way I come to this meeting. I am not vested in the trial, per se, other than to see if I have an option for my patients.

So my situation is that, as we see these patients, they come into clinic and they are in their twenties and they are in their thirties and they have had a clear-cut stroke. It is unequivocally a stroke, clinically and by MRI. They have recurrent events on medical therapy. They need an option.

At this point in time, in the majority of stroke centers in the country, the option of a catheter closure is not there, so the only option for these patients is surgical closure. My purpose in being here is to try and make the catheter option more widely available but in extremely controlled circumstances.

That is the reason for trying to put conditions on who is to be a candidate for closure. We are not trying to see we have proven unequivocally with a controlled trial that PFO closure is a good thing. We are trying to say, we have a population of patients that are difficult. They are not responding to medical therapy. We are closing the PFOs, not having recurrent strokes thereafter. Let's widen the indications but I agree with you absolutely that this trial does not answer all of the questions.

It doesn't even answer the majority of the questions. But it says, I, as a clinician, have a safer option than surgery now. That is what it tells me.

DR. MARLER: But the only data that I can see that is consistently and prospectively developed, very surprisingly, I think, to everyone involved showed that there was little difference between stroke patients with and without a PFO with regard to recurrent stroke rate, which means that there needs to be a better understanding of the pathological process and it does not, apparently.

Recurrent stroke in patients with PFO does not seem to deal entirely with the existence of the

PFO or not.

DR. FUTRELL: I think you are absolutely right. I agree.

DR. MARLER: Wouldn't a better controlled situation that you are describing be a clinical trial, itself, in exactly the subpopulation you defined, not some very large broad category of patients in which the benefit of closing PFO, I think, has been seriously questioned by a lot of people.

DR. FUTRELL: I think we would have some ethical dilemmas in randomizing a patient with a PFO, a young patient with stroke and PFO, to medical therapy when that patient has already failed medical therapy. I think, ethically, we couldn't do that.

DR. TRACY: Can we move on to Dr. Bailey, please?

DR. BAILEY: I have a number of comments and questions. I guess I do have a problem with language distortion in calling the primary--I think the label of the primary endpoint here was reduction of embolic risk. I think it should just be called closure of the hole, as was pointed out.

The data presented this morning relating

the follow-up information in the 49 in the pivotal cohort was compared to the underlying risk in a population; i.e., patients out in the community. I think the purpose was to try to show that the risk had been reduced to that level.

But I would like to see an upper confidence limit on the relative risk compared to the population. My guess is it is rather high. The point is not that you can't show it is higher than the population at large. The question is have you reduced it from what it would have been.

I accept the fact you don't think you can find adequate data in the literature, but I think, if you are going to show a comparison, it doesn't do any good to show that you don't have enough power to prove that it is worse than the ambient risk in the population. You need to show that it has been reduced.

So maybe I will stop and just let you address that.

DR. JENKINS: Actually, my colleague, Dr. Gauvreau, I am hoping, will be able to address that question. How do we get her?

DR. GAUVREAU: I'm here.

DR. TRACY: I am going to ask you to

introduce yourself by phone so that we know who we are talking to.

DR. JENKINS: I had made your disclosure for you earlier, Kim, before your presentation.

DR. GAUVREAU: Okay. I am Kimberlee Gauvreau. I was the biostatistician who worked on this trial. My understanding of the question was--it is a little bit difficult to hear, but the question was about confidence limits on the comparison to the general population cohort; is that correct?

DR. BAILEY: That's right.

DR. GAUVREAU: We did have sufficient data from the general population to actually do that. All I had were age and gender-specific drug incidence rates. So, instead, I chose to put the confidence limits around stroke in our cohort and compare that what would have been expected and experience the incidence rates in the general population.

DR. BAILEY: I think your expected numbers were something well under 1; correct?

DR. GAUVREAU: Right.

DR. BAILEY: If I am not mistaken, the upper Poisson confidence limit in a group would be

about three events. So, in other words, your upper limit on the actual risk of stroke is about 3 in 49.

DR. GAUVREAU: That's right. We observed 0, but the confidence interval was 0 to 3.7.

DR. BAILEY: Okay. So, 3.7 divided by the expected in the population would be your upper confidence limit on the relative risk.

DR. GAUVREAU: It would be close; yes.

DR. BAILEY: Which is about what, 50, 100?

DR. GAUVREAU: I don't disagree that the confidence limits are wide because of the relatively small sample size.

DR. BAILEY: So you haven't really demonstrated that the risk is not different than it is in the population. You have just shown that you don't have power.

DR. GAUVREAU: I mean, we have shown with the information we have that our pivotal cohort, that the incidence of strokes does not look worse than the general population. I mean, we did not see any.

DR. BAILEY: What about the four events that did occur? I suppose there isn't population data on that type of event?

DR. JENKINS: He is talking about the transient events, Kim.

DR. BAILEY: Yes.

DR. JENKINS: I think the answer is yes, there really aren't good population data. Also, I think that, as a measurement tool, transient events are a little bit softer as far as the reason for occurrence of events and stroke. So, actually, I, personally, prefer the stroke outcome data even though the numbers are very small and that does make the math more difficult.

DR. BAILEY: However, it is possible that those four events have the same mechanism, the mechanism we are looking for. So at least those are four events that were not prevented by closing the hole.

I would really ask to separate the two indications--I mean, the two indications of the shunt leading to hemodynamic or desaturation versus the embolic event risk. It seems to me this is two totally different reasons and to pool them is, like, you are borrowing the gloss from the shunt group to say that the whole group is benefitting.

I think we really have to talk about those two indications separately. It seems to me it is

very logical that closing the hole, if the reason for the original event was an embolus through that hole, then closing the hole should have 100 percent effectiveness for that mechanism.

Obviously, at least 60 percent to 70 percent of people with cryptogenic strokes don't have PFOs. Therefore, there must be lots of other unknown factors out there that are causing cryptogenic strokes. And many people are walking around with these PFOs that aren't having strokes. So it is reasonable, I think, to conclude that at least 50 percent, maybe more, of cryptogenic strokes are not caused by PFOs.

Still, if some of them are and you can't identify which ones are, it is conceivable that closing the hole will reduce the risk of strokes, but the problem is how much. I think that is where it is the cost-benefit tradeoff that is at issue here. We don't even have any idea what the benefit is. All we can measure is the risk.

What about surgery? I can appreciate that you have a dilemma if a patient is clamoring for surgery. They want to feel like they are safe. If they have surgery, then they feel safer, but we don't know how effective that is. I guess, if you

have a procedure that is less toxic than surgery, and it has the same unknown benefit, maybe very small, it is better to have that.

But is that a good reason for doing it? I think we need a randomized trial and I don't see why you can't randomize people given the uncertainty with respect to what the cost-benefit tradeoff is here. There are certainly complications of all these different strategies.

What about anticoagulation? What should you do after you close the hole? Given that the PFO was probably less than 50 percent likely to be the cause, even if it is cryptogenic, how do you know how much coagulation, whether to use anticoagulation arm. There should be three arms of a trial. You should have closure with anticoagulation, closure without anticoagulation and nothing, or anticoagulation alone.

DR. KULIS: Anne Kulis, again. I would like Dr. Kathryn Hassell, a hematologist invited expert, to address that issue.

DR. HASSELL: Good morning. I am Dr. Kathryn Hassell from the University of Colorado. I am the region's clotter, if you will. NMT is sponsoring my trip here today and covering my

expenses and time away from practice. I have no other financial interest.

This is an ongoing struggle from a hematologist perspective. These are people who have strokes. By definition, they have blood-clotting disorders. Now, I might not be able to name them. I might not be able to tell you what polymorphism they have, but, as opposed to the millions of Americans that have been discussed who have PFO, these people are different somehow.

The hematologist's perspective is that they have something stickier about their blood, evidence the fact that they get better on anticoagulation and risk reduction is observed. However, anticoagulation is imperfect and they have an additive risk factor of a structural hole in the heart where a small venous clot can become a devastating stroke.

Anticoagulation can be due to noncompliance or due to very avid hypercoagulable states, a prothrombotic will insufficiently control that risk. So, just for perspective, as I address the issue of clinical trial, device closure in a patient who has demonstrated their hypercoagulability by virtue of making a stroke

will reduce one mechanism of stroke.

As has been acknowledged by this panel, intuitively, that is absolutely the case. It is necessary in some patients, and we don't know in whom, and clinically we cannot tell, is it sufficient, I think, is the issue that has just been raised.

With regard to randomization, you have heard already the complexities of anatomical defects so one would, then, need to consider randomization not with three arms but risk stratification in each arm with those with a tunnel, those with a aneurysm, those with a simple defect perhaps based on number of bubbles they cross, the degree of shunt and, perhaps, even incorporation of desaturation as indication of degree of shunt.

Imagine the study size necessary to complete that study in a way that this panel would believe statistically makes a difference. Further, which anticoagulation would you select? Within the next two to three years, there will be another oral anticoagulant available. Around the time of the procedure, there is bridging with heparin or without, with low-molecular-weight heparin or

without, bridging to Coumadin or simply covering around the time of the procedure.

The point is we are at a point where clinically we are relying on the judgment of the physician caring for the patient as was done in the pivotal cohort to decide what is appropriate post-procedure anticoagulation based on a individual highly heterogeneous patient population.

I, as a person who works in the area of clinical research in thrombosis, cannot conceive of a study design that would appropriately randomize amongst variables that would involve anything less than several hundred thousand patients in order to answer the anatomical issues and the anticoagulation issues.

What the pivotal study did was simply ask clinicians who know their patients to say, you know what; device closure is not sufficient. I am going to maintain warfarin therapy, which was done in 20 percent of this cohort versus, I think, really, the issue was paradoxical embolus. I can't find anything else including calling my friendly hematologist for an assessment of hypercoagulability and aspirin will suffice.

I would submit to you that the physicians

in the study did a great job because in this thrombogenic group of folks, only one person had a thrombus out of 49. I would have predicted it to be much higher based on what I believe to be true which is these people have sticky blood because they made a thrombus.

So I think it would be extraordinarily challenging to devise a study that would be powered sufficiently to answer the complex interactions that this cohort represents.

DR. MARLER: So, I get back to my question. What is this cohort?

DR. HASSELL: This cohort is a heterogenous group that is characterized by basically three things. One is the person who has a shunt. I would agree, in terms of analysis, one would dispense with those is the way I think of it as a hematologist because they haven't demonstrated thrombosis yet.

The second are persons who had, by characterization on the slide you have seen, recurrent thrombotic events. There were six of those. The third are persons who have contraindications as perceived by their care providers to anticoagulation therapy which distinct

from WARSS in which the inclusion criteria meant you need to be a Coumadin candidate.

As you see depicted on that slide--I apologize, I should find you the number--they talk about a person whose lifestyle precluded warfarin therapy, who was difficult to control warfarin therapy, who had other contraindications as perceived by the care provider and the patient to chronic anticoagulation.

DR. MARLER: Do you think warfarin works better than aspirin in these patients

DR. HASSELL: I believe, theoretically, as a hematologist, that if at issue today is venous thrombosis crossing a septum and causing stroke, that aspirin unequivocally is insufficient to control paradoxical venous embolization because it does not control venous disease.

I think, in terms of the WARSS data, as you allude to, or this group in particular, that issue is poorly characterized and unclear because they are lumping people together who clearly have venous thrombotic disorders that we can't yet identify, persons who have other vascular risks and persons who have arterial risks.

I think until we better define what the

mechanism of stroke is, we are left with broad generalizations. But, for persons who have paradoxical venous embolism, there is no doubt in my mind that warfarin is better. The problem is we don't know who is paradoxically embolizing.

DR. TRACY: Dr. Bailey, any additional questions?

DR. BAILEY: I didn't understand exactly what the reason was why it would be so complicated and require so many patients to demonstrate reduction in embolic risk in a high-risk group. Why does it require hundreds of thousands of patients? Do they have high risk of embolus? If they have a high risk of stroke, and if there is--if PFO is the primary cause and you recruit cryptogenic stroke patients with a PFO, it should abolish stroke. So it should be very, very easy to see that in a randomized study

DR. HASSELL: Yes, although, Dr. Bailey, I think what we are trying to do is we are trying to identify persons who are appropriate for closure; that is to say, there have clearly been defined, especially since the WARSS data, persons who are thought to be at higher risk for paradoxical embolism or even formation of clot within their

PFO.

So those are persons with long tunnels, persons with redundant tissues and atrial septal aneurysms. So I suppose one could conceive of, perhaps, two or three groups, then, a small shunt with few bubbles that cross, a shunt that is characterized by a large number of bubbles that cross and then one with complex anatomy, and then randomize each of those groups to chronic warfarin, perhaps to aspirin, as someone has just alluded to, perhaps, or to closure.

So you are looking, then, at six groups--or have I got my math wrong--nine groups; I apologize.

DR. MARLER: So, if you don't know which of these groups the treatment is effective in now, I am confused how you can advocate its use.

DR. HASSELL: If you are referring to closure, I have no doubt that there are persons who make venous thrombi that are clinically otherwise unimportant if their septum is closed; that is, they go into the lungs, they are screened out and lysed by the fibrolinic system in the lungs, that when they have a patent foramenal valley, especially with complex anatomy or shunt, become

potentially devastating cerebrovascular events.

That is obviated by closure. It cannot occur when closure is effective.

DR. MARLER: But, by testing each of the selection criteria in a separate trial, isn't that expressing a lack of confidence that you know who to select that you think will benefit?

DR. HASSELL: I am not proposing a trial. I think the issue is if you want to answer the question of who is most likely--see, I think the potential warrants, in a low-risk procedure, obviation of a route of stroke. But I was asked to address the issue of clinical trial.

To answer the question scientifically, one has to address each of the potential variables, as has been suggested by the panel. I would not do such a trial.

DR. BAILEY: And why not

DR. HASSELL: I would not do such a trial because I do not believe that you can get sufficient numbers of patients to answer the question to the satisfaction of the issues raised. You can't answer--

DR. BAILEY: Aren't we anticipating a huge benefit in reduction of risk?

DR. HASSELL: We anticipate a benefit in reduction of stroke because you eradicate one mechanism of stroke. That, in mind, justifies the procedure.

DR. BAILEY: But, if it is a huge benefit, then a small sample size is required

DR. HASSELL: Even if it is a small benefit, and I don't know how to estimate that because I can't tell who is paradoxically embolizing.

DR. BAILEY: If it is a small benefit, though, then you have to weigh it against the risk of the procedure

DR. HASSELL: That is correct.

DR. JENKINS: There is one other issue with the trial design, I guess, that I would just like to point out because I think it is pertinent to the way we presented the information. I think the typical trial that is being contemplated takes patients who seem to have a high attributable risk of their stroke from their PFO and randomizes them to medical treatment or to device closure and follows them for 24 months and counts stroke rates over the 24-month period.

I am sure it is because of my pediatrician

bias, and I will not apologize for that, thinking about this more in young patients rather than in old patients, the health status of those patients at the end of that 24-month observation period, in my mind, is really not the same.

One group of patients will have accomplished closure of their PFO and will be left with the rest of their medical-health state and the other group of patients will still have their PFO and still be on medical treatment.

One principle of randomized trials is that the outcome assessment at the end of the observation period has to be equivalent. At least from a pediatrician's point of view, with 50 years or more ahead of these people, I do not see those health states as equivalent.

On the other hand, to deal with the issue of baseline risk, appropriately from a trial-design point of view and all the multiple confounding factors, randomization is clearly the correct trial design to balance the two groups out. So I find the whole discussion very problematic from a separate point of view than what has just been told to you.

DR. BAILEY: I'm sorry; but I didn't

follow what your problem is with the health status, again, at the end of the--

DR. JENKINS: Because I do not see, as a pediatric, in a young person, at the end of a 24-month observation period for a trial, if one group of patients still has a PFO and is still on medicine and has the additional ongoing risk for the rest of their life from that state to be equivalent to the closure arm.

So, to me, the only two--

DR. BAILEY: But you are assuming that the risks are worse in that group

DR. JENKINS: I am assuming that, at the beginning of this trial, someone thought you either needed Coumadin or aspirin or you needed to have your PFO closed; that's right, that you could create entry criteria such that you would get in.

DR. BAILEY: If PFO is not the only reason for a cryptogenic stroke--let's say, 50 percent of the time it is the cause.

DR. JENKINS: That's right.

DR. BAILEY: Then what gives you the right to withhold anticoagulation after closing the PFO? Why shouldn't those patients be on anticoagulation if they have had a stroke. We don't know that

fixing the hole, plugging the hole, will solve the problem.

DR. MARLER: I thought we just heard that you were going to select patients that were at increased risk of thromboembolism.

DR. TRACY: The unaddressed issue is the indication for anticoagulation following closure of the anatomic defect. How was that determination made? There were eleven patients that had some definite contraindication to anticoagulation. That implies that 30-whatever did not. Why determined discontinuance of antithrombotic or anticoagulant therapy of those patients.

DR. JENKINS: It wasn't determined by the study. It was done by the treating physicians. I would imagine that the inputs to that discussion were eradication of the PFO, the potential for additional diagnoses that become more likely once the treating physicians knew that the PFO had now been closed, the occurrence of any of these transient neurological issues that raise red flags for clinicians who tend to behave conservatively, and whatever the other baseline health states were. As an example, patients who had previously defined hypercoagulable states would not have had their

at

treatment stopped.

DR. ZIVIN: I believe that we have clinical equipoise in this situation and, therefore, if you have identified a group of patients who you believe that you can identify prospectively a set of criteria that would be usable for running a clinical trial, regardless of how small that treatment group is, and then show therapeutic efficacy, you could come back to this group and get approval for that device.

Under these circumstances, we have no prospective data and no indication for treatment of anyone.

DR. TRACY: Dr. Bailey, were you completed with your questions?

DR. BAILEY: Yes.

DR. TRACY: Unless there is a comment on that last comment--

DR. FUTRELL: There is no question that we have this group of patients that is failing medical therapy. Those patients are going to surgery at this time. The surgeons have a little advantage over device because they don't have to get their treatment approved. Those patients are going to surgery.

I don't disagree with you at all that we don't have nearly the data we need for a generalized application. We need to understand much more about paradoxical embolism. We need to understand more about the anatomy of PFO.

What I am struggling with, as a clinician, is to find a way to close this hole in patients who are failing other treatments or who are at risk for those other treatments without sending them to open-heart surgery. In the meantime, I suggest we start working on the trial that is going to take care of the standard patients but that we not deny the complicated patients a nonsurgical treatment in the meantime.

DR. KULIS: Anne Kulis, again. I would like Dr. Carole Thomas, if she could address this issue further.

DR. THOMAS: I am Carole Thomas. I direct the Stroke and Intensive Care Program at Hahnemann University Hospital. I am a neurologist and I have no financial connection with NMT. They have paid my travel and expenses for the day here.

As a treating stroke neurologist who happens to see a large percentage of actually young patients with stroke, who have had a stroke, who

have been referred to me from various sources and have found to have a PFO and, many times, no other source because of their young age, between twenty and fifty years old, this is a tool that has the potential for being used in these patients who are poor candidates for anticoagulation because of lifestyle, child-bearing issues and also because, quite frankly, they are very resistant to being on anticoagulation or even, at times, antiplatelet medication.

This is a defined high-risk group that also would be resistant to having a surgical procedure, an open-heart procedure. These are patients whom I define as being high risk for having a recurrent stroke and also high risk at having significant, both social and economic, consequences of a second stroke after either failure of medical therapy or lack of basically compliance with medical therapy.

These are not your typical patients that I would put into a randomized clinical trial between antiplatelet, antithrombotic versus procedure and often would not actually qualify for that level of clinical trial, either because of child bearing, because of compliance and what not.

I think that it is important to understand that we are not talking about this indication for every patient with a stroke and PFO. We are talking about this indication to broaden it slightly so that we can have it at our disposal when we find an appropriate patient who we think would benefit from having this closed.

Also, there are many times when I have patients who, despite having their PFO closed, I will maintain them on either antiplatelet or antithrombotic therapy as their clinical situation dictates. So, simply having a PFO closed does not mean that they cannot be on antithrombotic treatment afterwards or antiplatelet. That is really individualized for each patient and individualized for what they need.

That is the other thing that is important about this is that these patients are so very diverse in what they actually need which is why our recommendation is also to have them evaluated in a stroke center with a treating stroke neurologist who is accustomed to doing extensive workups to be sure we have covered all the bases and why the stroke occurred and how to take care of the patients from then on.

DR. LAZAR: If you could put them on some form of medical therapy after closure, why close them in the first place if it is not established that the closure, in fact, is related to the stroke in the first place?

DR. THOMAS: Because my job, as a stroke neurologist, is to limit risk factors. Actually, that is all we ever do. I can treat a few of them with TPA but, for the most part, we are talking about secondary prevention of stroke and what is that all about? Treating hypertension, treating diabetes, operating on carotids, giving Coumadin for atrial fibrillation and closing PFOs.

It is all part of the limitation of risk factors for second stroke and I hate strokes.

DR. MARLER: Each of the risk factors and interventions that you mentioned have been well demonstrated to have serious risks and serious benefits. It is very difficult, in the absence of good controlled clinical trials to determine when the benefits outweigh the risks.

In many trial, be it the EC/IC trial, the WARSS trial, itself, conventional clinical wisdom or what was obvious and apparent as a mechanism, when treated and followed carefully and looked at,

was not shown to be effective.

So, PFO stands out in your list of treating risk factors for doing exactly what stroke doctors should be doing, every doctor should be doing, actually--stands out in that it isn't the one that is, as near as I can determine, that is really backed up with a serious estimate of the benefits as well as the risks in measuring the balance.

Would you agree with that?

DR. THOMAS: I think that, basically, looking at evidence-based medicine, clearly, there is some lack of evidence but also realize that the patient population that we are currently talking about would not be entered into any clinical trial, just as the high-risk carotid patients were not entered into the NASCET trial.

A lot of the perfect patients who get into these clinical trials are not the patients that we see every day that we need to make a clinical decision on. While there is, certainly, a need for more data, one of the ways to obtain that in the higher-risk patients is to be allowed to implant these devices and follow the patients.

DR. TRACY: Let's move on to Dr. Laskey,

if we could, please.

DR. LASKEY: By the time we get to the middle of the table, it gets to be tough going so I will be brief. This is not a trial. This is a prospective longitudinal observational cohort study of a bunch of patients who had a device skillfully implanted and were followed. But there are no, as we stated before, prospectively defined entry criteria, selection criteria, management criteria and so forth. So that is disturbing because that is a new one for me as a panel member.

The second point is that this is very representative of what happens with selection bias. This is a quaternary referral center. Patients are referred in with the expectation of having a procedure. They generally will have a procedure and they probably need that procedure. But the difficulty we are having here, and the sands are shifting, are going from a patient population which, by IFO, is fairly benign to what I have heard for the last hour which is pretty sick.

What I would like to know is do you have any idea of the number of patients in the box at the top of the page that is not at the top of the page? How many patients were screened or

considered or rejected or not selected? What is the generalizability of these findings? Even though we are having a tough time accepting the validity of these findings, how generalizable are these patients and what is the fraction of the n in the top box, of the total number of patients you saw at this center that were sent for this procedure?

DR. JENKINS: I am sure I am not going to have a perfect answer to your question, and I should just clarify, this is not actually a single-center dataset the way the one that you all saw last year that was similar was. Most of the implanting centers have closed PFOs as part of this trial.

We don't really know how many patients were found to have a PFO that was thought to be an attributable risk factor for them and were never sent to an implanting center. We do know that, of the patients who were sent and referred to implanting centers, that you were not eligible for our study if you were eligible for ongoing regulatory trials that we were running which were the PFO randomized trials that were ongoing at the time that this was as that was an explicit

exclusion criteria from our trial.

We also know that the vast majority of patients that were turned down by peer review in this study were turned down for the PFO indication for not meeting the entry criteria. We actually meant to quantify it for you expecting this question and I am afraid I didn't do that, so I will have to go by memory.

But, of the people who were formally presented as opposed to informally discussed, there are probably at least 25 percent of the patients were turned down by the peer-review team. The peer-review team. The peer-review team was actually a comparison to surgery, not a comparison to medicine, by design of our trial.

The peer-review team struggled a lot about which patients to pass and which patients to avoid. They turned down a large number of patients for the PFO indication for not meeting the apparent high-risk criteria.

Generally, the patients who were included were patients who had had recurrent events and were an absolute contraindication to medical treatment as defined by the treating physicians who were sending the patients forward and as assessed by the

peer review.

So I am not sure if that is helpful but, as far as the entire eligible population, and who actually made it into this 49-patient cohort, in terms of a numerator and denominator, I am not really sure, but there were multiple hurdles to overcome in order to get there and all of them really had to do with the fact that people believed that this PFO was a risk factor for the patients and that the alternatives were not acceptable.

DR. LASKEY: I appreciate that, Kathy. Thanks. It just puts some boundaries on the magnitude of this problem, but it is also disturbing to see that the field, some portions of the field, have moved from risk factor to causation. It is a risk factor. As my statistician colleagues tell me all the time, and you always have to put into your manuscripts, it is "associated with." It is not causal, and we are obviously grappling with that issue and there is no data to support causality here even though we all understand the thinking.

The event rates, I just wanted to see if you agree with the perspective that I put on them. I did some very naive confidence intervals for the

four on 49. You had four events in the 49 patients in the pivotal cohort study with an event rate of 8.1 percent but confidence intervals that go from 3.3 to 19.2 percent.

Did you go so far as to put some precision on your point estimate?

DR. JENKINS: Kim, do you want to address that? I think that he is including the stroke plus the TIA rates.

DR. LASKEY: The four on 49; right.

DR. JENKINS: That would be stroke plus transient events.

DR. LASKEY: Correct.

DR. JENKINS: Kim? Are you there?

DR. LASKEY: She may not be. But then I did the same with the follow up in the 87 patients after device implantation. It wasn't clear whether these were one-year cumulative event rates or not but I got nine on 87.

DR. JENKINS: Those are throughout the entire period of follow up.

DR. LASKEY: So that's everybody.

DR. JENKINS: Yes.

DR. LASKEY: Okay.

DR. JENKINS: We didn't define a time

point. We took all the data that we had.

DR. LASKEY: Cumulative. It is interesting, the upper limit there is 18.5 percent, the same as the--

DR. BAILEY: But that was for a half a year median follow up.

DR. LASKEY: Right.

DR. BAILEY: So that is for a half year.

DR. LASKEY: Correct. Again, I am getting a picture that there is a sizable spread here with a low event rate, but the worst-case scenario is an 18, 19 percent event rate. The data are not inconsistent with a 19 percent event rate in patients that had a device implanted. Is that correct?

DR. JENKINS: Kim, the questions are about the wide confidence limits around the stroke plus TIA rates.

DR. GAUVREAU: Yes; I'm sorry. I got disconnected. It was the four out of the 49 patients. So the confidence limits would be about 2 to 19 percent.

DR. LASKEY: Okay. That is distressing.

DR. BAILEY: Again, 19 percent for half a year.

DR. LASKEY: Right. The risk, the high-risk, nature of the patient population in the pivotal study; high risk for what? There is a lot of comorbidity here. You have some fairly sick congenitals. You have some fairly sick just medical comorbid conditions. You have high risk for stroke and then high risk for other bad things, or what?

DR. JENKINS: We generically call this study our high-risk study. I think a lot of people in the PFO context have assumed that that meant high risk for recurrent stroke because, of course, that is usually where stroke studies go.

The actual term "high risk," because of the nature of our study, is high risk for surgery.

DR. LASKEY: Okay; it is very misleading. There are three kinds of risk terms being tossed around, at least three being tossed around here. So it would help if they were more fine-tuned.

Then you have an intriguing group of patients with hemodynamic derangement. What was that? Was that just the elevated PVR group?

DR. JENKINS: I'm sorry; say that again?

DR. LASKEY: The inclusion criteria were the patient had one or more cardiac defects which

are ascertained by the procedures outlined to result in sufficient hemodynamic derangement to warrant intervention. That wasn't clear in the description of the patients. What kind of hemodynamic derangements?

DR. JENKINS: I think, in most of these cases, that was simply the presence of the PFO with right-to-left shunting with whatever the pathway that happened previously was that led people to think that that was an embolic risk factor, except for the cyanotic patients. That is how the criteria were applied.

DR. LASKEY: To a hemodynamicist, that is not a derangement. They were not circulatorily fragile, in other words.

Two quick things. Your patient brochure is, on the one hand, I think, way over the head of the average informed patient, probably parent as well. So I think there is a lot of jargon, a lot of technical stuff in here, that really needs to be made a lot clearer, shall we say.

Then, of course, there is this whole leap of deductive logic here between risk and causation. That is just throughout here. I find it insidious. I find it coercive. I think that that should pick

up on some of the flavor of today's discussion, at least the concerns that we are having up here.

Then, finally, our old friend the fracture rate. I had the privilege of being a panel member during your prior presentation in a terribly, terribly sick group of patients that really needed compassionate care and warranted the risk of a number of device-related mishaps.

I am not sure that that is the case here. I was struck by the fracture rate specifically for the PFO indication relative to an ASD indication and the fracture rate in the PFO cases consistently exceeded, almost by two, the fracture rate in the ASD group. Why is that and what do you think that means for thirty, forty, fifty years of having this device implanted?

DR. JENKINS: Before we talk about the clinical relevance, can I just ask Kim to address that issue because we have looked at it in enormous detail.

The question is about the apparently higher fracture rate in the PFO indication when we have looked at fractures in the overall cohort. Could you comment about that?

DR. GAUVREAU: Yes; I can. What we have

found is that fracture rate is highly associated with device size. PFO patients tend to get larger devices. When I control for device size--

DR. JENKINS: Kim, we lost you.

I'm sorry; but I would really like to have her explain this to you because we have spent a lot of time looking at, from the time that was first identified. Also, it looked slightly worse in the STARFlex than in the CardioSEAL so we paid a lot of attention to it.

DR. GAUVREAU: As I was saying, the fracture rate on PFO patients is due to larger devices in those patients. When we control for device size, that association goes away and PFO patients actually do not have a higher fracture rate than ASD or the other lesions.

DR. JENKINS: You have done that by stratified analysis, but multivariate analysis, on CardioSEALs and in STARFlexes?

DR. LASKEY: She has disappeared.

DR. JENKINS: She has.

DR. LASKEY: That is the concern. I know when it goes into the black box of multivariate analysis, things can come and go. But the point estimates look fairly striking.

DR. JENKINS: They actually go away. Actually, any time that people report fracture rates, it is very important not to look at overall rates because the device-size effect is so great.

In the STARFlex cohort, it is a little bit less because, as you see, there are only the three device sizes, the 23, the 28 and the 33, whereas, when you add in the 17s and the 40s by CardioSEAL, it is dramatic.

We are a little bit disappointed in that the fracture rates in STARFlex do not appear to be statistically lower than they were in the CardioSEAL device.

Switching now to the other aspect of your question which is the clinical significance of device-arm fractures, I think that, early on, there was a lot of concern that device-arm fractures would result in device destabilization or other problems. The fracture rates were actually substantially higher in the Clamshell I cohort than in the late cohorts, and so there are quite a few patients that we are following with device-arm fractures.

The vast majority of fractures are completely clinically silent. The fractures tend

to occur as is in the submission at time points after the device has begun to endothelialize. Having said that, there is a small number of patients who do suffer the consequences of device-arm fractures.

In the original clinical trials with Clamshell, there were seven patients in our cohort of 508 cases who had fracture-related events. To date, in the entire follow up, and I can only speak to our experience in Boston but Anne can speak more broadly, for both the CardioSEAL series of cases and the STARFlex series, there is only one case that I am aware of, and it was on Boston, who had a fracture-related event.

It was, again, a friction lesion in the region of a protruding arm in a device that was detected because of symptomatology and was removed. The events to seem to occur occasionally but are really quite rare.

Have there been other fracture-related clinical events from CardioSEAL or safety devices, other than the one that we reported to the FDA from our trial three or four months ago?

DR. KULIS: I think, from a commercial standpoint, globally, both CardioSEAL and STARFlex

have been on market, as said earlier, since 1997. The product complaint rates are similar to what Dr. Jenkins said, that events associated, adverse events associated, with fractures are, indeed, quite rare.

DR. LASKEY: Thank you.

DR. TRACY: Dr. Lazar?

DR. LAZAR: Just a quick follow up on the adverse events. I always worry about underreporting adverse events. So, for example, only MCA territory strokes were considered adverse events from a vascular point of view? So, if a patient had a brain-stem stroke, how would you classify that?

DR. JENKINS: No; that's not true. They were just categorized that way. All the events were ascertained and all the events were in front of you.

DR. LAZAR: But they were not considered strokes. On the slide, I thought I saw it said, MCA territory only.

DR. JENKINS: That was only in the second line which was of the transient events, we tabulated classic TIAs, transient visual changes, and other. We also provided you with a complete

description of those events in the panel pack.

That might actually not be a bad place to perhaps the chair of the safety committee who has reviewed the thousand events for this trial to maybe comment on what the safety committee did. Would that be helpful?

Could we invite Dr. Hougen, who is the chair of the safety committee, not just for the PFO cohort but for the trial overall to just maybe clarify for you what the safety committee did do.

DR. HOUGEN: Good morning. I am Tom Hougen, pediatric cardiologist at Georgetown. I have no financial interest in the company, in this device, and I have not received any expenses for being here today, either. But I am glad to be here today to answer the panel's questions.

The question is, please?

DR. JENKINS: Tom, I think that people are used to trials where only certain events are ascertained. We have told the group that we have made a very comprehensive ascertainment of adverse events similar to a drug study and that you have reviewed them and classified them in terms of seriousness and attributability.

Could you just say what the three of you

have done?

DR. HOUGEN: The other main member of the safety and data monitoring committee is Dr. Ron Lauer from the University of Iowa. He and I have met consistently about every six months for about five years, now, I think, reviewing every adverse event that the study group has listed and they are extensive. The current coordinator of this is Amy Britt and she is also here in the audience.

Dr. Lauer and I have been consistently impressed with the detail of all the adverse events and, in some occasions, have asked the study group to almost not list all of them. They have been very detailed and particularly important in the pediatric group, in the younger patients, that have a number of problems that come up, returns to the emergency room for a variety of seemingly unrelated events that--the trial group has listed these very, very carefully.

As you can see from the high-risk nature of these patients, they have multiple medical problems. Every event associated with their medical problems is listed and is reviewed by our committee. We assign a seriousness. We edit what the committee has given us, or at least the study

group has given us, and we have agreed most of the time, but not always, on the seriousness of the events.

But Dr. Lauer and I have looked at these over the years and they are very extensive, from minor illnesses in a child to problems with diabetes control or other related problems in older patients.

Other questions, please?

DR. LAZAR: Were there follow up or serial neurologic exams that were explicitly scheduled throughout the patient's participation?

DR. JENKINS: No. There were, as we have said, I believe--several times, we ascertained the information periodically but we did not specify specifically neurological testing or testing for any of the other indications except for what I had showed you earlier.

However, if neurological follow up was done by the patient's own doctor, a new diagnosis came to light, those would have been ascertained by our catchment.

DR. LAZAR: So there wasn't central adjudication of neurological events.

DR. JENKINS: This is not a neurological

endpoint committee. That's correct.

DR. LAZAR: The reason why I asked the question is how you interpret endpoints or adverse events. There is one case I read here in Clamshell, a cohort, where a patient was described to have had an event which was described as a TIA and was classified as a TIA by the committee, but then goes on to say that the patient had an infarct on the scan but then was considered still to have a TIA. Was it a TIA or a stroke?

DR. JENKINS: The Clamshell cohort wasn't really reviewed by this, as I had mentioned previously. It is a very different quality of data than the CardioSEAL or STARFlex cohorts. I would be interested in that event. I would also be interested to know, since all these patients often had strokes as their indication, whether it was not considered to be a new stroke or what.

But, if we have misclassified it, then that is our error.

DR. TRACY: Dr. Becker, please?

DR. BECKER: I have a couple of questions and comments. Firstly, it seems like the medical comparator group that everybody refers to as warfarin, is this device placement safer than

warfarin. I would submit to you there is no data to suggest that warfarin is any better than aspirin at this point, with one exception, and that exception would be in people who have defined hypercoagulable states.

In those patients, you could make the argument, why not just continue to anticoagulate them because they are going to be anticoagulated after device placement anyhow. The one question I have for you is there any data from your group or anybody else who has got experience with the device on what the risk of device thrombosis is in people who have hypercoagulable states.

The second question I have has to relate to the fracture problem as well. These devices, presumptively, are going to be placed in young patients. These patients are going to have a very long time with the device in place. It looks like the risk of fracture increases as time goes on and, in the pivotal cohort study, you have very few patient years of follow up.

In the pivotal-cohort study, you have very few patient years of follow up. If you go back to the Clamshell study, as you mentioned, there were some problems with friction of the myocardium, or

endocardium. So that is a little bit concerning, and what do we tell patients about the longevity of this device.

Finally, there is at least one group that believes that some of the stroke risk associated with PFOs doesn't have to do with paradoxical embolus but with this concept of atrial vulnerability. There seem to be a lot of atrial ectope in placing these devices. I am wondering if someone from the study could comment on that and also comment on how many of these patients had prolonged Holter monitoring prior to device placement to rule out arrhythmia as a source of original embolism.

DR. JENKINS: I think all three of these are very important issues. The first one relates to the occurrence of thrombus on the device and, particularly, to the occurrence of thrombus in a hypercoagulable patient as, perhaps, a way that the device closure could actually make patients worse or put them at risk.

I am going to actually ask Dr. Hassell to comment from her point of view as well because I think she has spent a lot of time thinking about this.

Interestingly, in our cohorts of patients, the ones that I follow, we have really only very rarely seen thrombi associated with the devices. The instances where they have occurred, at least in my clinical judgment, are often very confounded by arrhythmias that seem to be previously either know or, in some cases, unknown at the time that the thrombi have occurred.

Having said that, however, we estimate that, in our cohorts overall, some type of thrombus or friction lesion may have occurred in 2 percent of cases throughout the follow-up period. I do not mean to imply that those are all symptomatic or cause a problem, but that they were, at some point, detected.

In the other trials that have been done with the device, sporadically, these types of thrombi appear to crop up occasionally in a little bit of an idiosyncratic fashion. I have had a hard time making a firm opinion about it since I haven't seen it in my own trials, so I think having noted that, I would like to ask Dr. Hassell to talk about that.

DR. HASSELL: Firstly, by way of data that are available, I call your attention to the amended

piece that was sent to you after the initial application materials, on the last page. I have had the privilege of reviewing the complaint logs for the company, NMT, that reflect thrombotic and other complications over 8,000 devices, approximately, that have been place.

In the second-to-last paragraph, on Page 6 of that amendment and what I can tell you I have seen from the data is that thrombosis has been seen in the CardioSEAL devices and also in STARFlex of 0.2, 0.1 and 0.7 percents in various years, 2001 and 2002, or in quarters in those years.

So it is striking to me that the thrombosis rate that is recognized principally because of clinical events, although, in some of these cases, because they have had surveillance echocardiography, is below 1.0 percent. Now, this may reflect the fact that those cohorts are not as high risk a group as are characterized in this pivotal study and these are persons, as we have already discussed, that have either challenges with anticoagulation or actual failure of anticoagulation which may not be broadly reflected in those 8,000 patients and, thus, a higher risk percentage of 1 or 2 percent.

What we do not know is how many persons, even who have developed thrombosis, have hypercoagulable states. When one looks at the literature, persons referred for closure, hypercoagulability is frankly poorly defined. Testing is sporadic and often incomplete and there is an assumption which, with due respect to the concern about causality versus association, that often neurologists and cardiologists stop when they find an PFO and make an assumption about the mechanism of stroke in a young person.

So there are very few data that have comprehensively addressed the issue of hypercoagulability in the patients in general, never mind in the persons, the rare and small number of persons that actually go on to thrombose. In that dataset that are reflected in this paragraph, I have seen hypercoagulability testing done in a very small percentage of persons.

For example, in three people who were assessed for antiphospholipid antibodies, two of the three had them in this thrombosis database. So there are all sorts of hints and nuances about the possibility of hypercoagulability in patients who actually thrombose the device, as rare as that

event is, but there are really very few data about whether or not hypercoagulability exists.

Now, remember my premise, these people are all hypercoagulable at some level because they have made a pathogenic thrombus. The problem is that represents a broad biological spectrum a large percentage of which we cannot identify with specific testing because we are only learning how to identify stick blood or those hypercoagulable states.

DR. CARABELLO: In this study, we had one device explanted because it had thrombus on it.

DR. HASSELL: Yes.

DR. CARABELLO: One would have guessed that patient would have had the dickens studied out of him. he has already had the device planted to begin with and now it is being explanted for yet more thrombus. What do we know about that patient?

DR. JENKINS: He also had thrombus in the rest of his atrium in the setting of recurrent atrial fibrillation. I apologize. I should know what was done at Columbia to look for hypercoagulable state but I actually think, in his particular instance, or her particular instance, the thinking at the time was that it was because of

the arrhythmia. So I don't actually know how that patient was studied.

DR. CARABELLO: So the device was explanted because--if the clot was due to the arrhythmia, then why was the device--

DR. JENKINS: That was the decision that was made by clinician. They were very fearful of the thrombus on the device and the recurrent atrial fibrillation and the physicians, along with the patient, decided to go for explant. At explanation, in that particular case, there were thrombi in parts of the atria remote from the device as well, as I recall.

DR. COMEROTA: How was the PFO handled in that case?

DR. JENKINS: It was post-surgery.

DR. BECKER: Do you know how many of the patients actually did have Holter monitoring prior to PFO closure?

DR. JENKINS: No. I mean, again, we didn't specify that or look for it. I think it is very interesting the amounts of arrhythmias in this older group--older from a pediatrician's point of view--group of patients that were found afterwards.

I certainly raises a flag to me about the

prior screening in this particular regard. There is also an issue about whether devices can cause arrhythmia or whether devices could cause sudden death. We have also looked at that in our cohorts overall and do have some information about it.

Generally, the way the datasets are here fairly consistently is if new arrhythmias that had never been diagnosed occurred in the transient period after device placement, they are classified as due to the device which is why you see those device-related events cropping up.

One of our fellows had presented an abstract looking at the issue overall and had found that there are transient rhythm disturbances after placement, particularly in the V

criteria they went into the control group.

My question is were there patients that did not fit the anatomy and, therefore, would not be an EBE candidate that went on to not get any surgery at all? That ended up not getting an open operation because perhaps the local investigator felt that aneurysm was too small; they were too sick; or there were some other issues. Did you have a group of patients out there that didn't get operations? I know in other groups sometimes some information comes from a group that doesn't get the procedure during the period of time, and I wanted to know if there was a small number of patients, a large number of patients, or if you know of any patients that started off and then didn't get any procedure whatsoever.

DR. MATSUMURA: We don't have data on patients except for those that were consented for the study. I think that breakdown is in there. None of those patients, to our knowledge, did not get a procedure or had aneurysm rupture. I didn't show it in the presentation but we do have the deployment success in the control group and 100 percent of those patients, all 99, had their surgical graft placed. There were no aborted

clearly documented.

The reason I am asking this is we look for hypercoagulable states all the time in these patients and find them in really a minority group. In this 49-patient cohort, there is only one patient that is listed as having a hypercoagulable state.

In your experience, how many patients with true hypercoagulable states fail Coumadin that is adequately given and adequately monitored

DR. HASSELL: To answer the question specifically firstly. Antiphospholipid-antibody patients have a 1 to 2 percent chance per year of recurrent event despite therapeutic warfarin with an INR of 2 to 3. It is ill defined for persons with a higher INR.

Warfarin failure in virtually any other setting is uncommon when a therapeutic INR is maintained. But, in my Coumadin clinic of 300 persons on any given day, 20 percent are subtherapeutic. So it is not an issue of can warfarin work but can we make warfarin work in patients.

So even though the hypercoagulable state, per se, is responsive to warfarin, it is a

challenge to maintain adequate anticoagulation. For a perspective at our center, we have been referred more than 50 patients for potential closure for PFO. When I screen for hypercoagulability, 55 percent have antiphospholipid antibody syndrome.

I would submit there are genetic polymorphisms out there that every person, for example--and I recognize this represent's what I call Hassell's dogma--but an evolving concept in the world of hematology is that every person with A-fib who has a stroke has some polymorphism or change in their blood such that the majority of persons with A-fib don't stroke at the time they develop the atrial fibrillation, but a small, clinically important, percentage do.

So I would just mention it again as my background bias as I answer your questions is that every person who clots has sticky blood to some degree that is different from the general population, whether it is definable or even needs to be defined, and should be sought out, I think, as a different and the appropriate question.

DR. TRACY: Dr. Becker, any additional questions?

DR. JENKINS: Dr. Becker, your fracture question wasn't answered. Did you want that answered? The question about device-arm fractures. You asked about the ongoing occurrence of fractures and the longevity of the device.

First of all, actually, the ongoing fracture detection rate in the short cohorts of patients, you do continue to see ascertainment of fractures at the time points of assessment. But, actually, in the Clamshell cohort, where we have much longer longitudinal data, after the two-year initial period, ongoing detections of fractures is actually exceedingly rare. One of the whole points of that cohort was to make that determination.

There is also additional engineering information about the longevity of the device that we could share with you with the engineer, if you would like that.

DR. BECKER: I guess I am not so much worried about the longevity of the device but its effects on the endocardium over the long term.

DR. JENKINS: As I said previously, even in the fractures that have occurred, with the rare exceptions we have already talked about, the late clinical events occurring from that appear to be

quite rare.

DR. FUTRELL: Dr. Becker, one other thing, when you asked about the atrial fibrillation, there is some information being gathered from centers who are operating under the HDE approval. It is interesting that, even when Holter monitors are done in advance and we are showing that patients are not in atrial fibrillation, there is transient atrial fibrillation turning up in 2 to 4 percent of patients after CardioSEAL placement. But it has never been permanent and it has never been associated with a clinical event as far as an ischemic stroke.

DR. KULIS: Anne Kulis, again. I would just like to follow up a little bit on the question about device thrombosis, or thrombus on the device. I would like to ask one of our invited experts interventional cardiologists that have experience implanting under the HDE approval to perhaps address the issue of thrombus on the device, the infrequency of it, and possible examples of treatment.

So I would ask Dr. Reisman, Block, Landzberg or Palacios if they would please come up to the table.

DR. REISMAN: Good morning. Mark Reisman from Seattle, Washington. I have no vested interest or conflicts. NMT is supporting my travel and expenses here.

I am operating under the present HDE. Under that HDE specifically related to thrombosis, we have had one patient, actually, who has developed a thrombus on the right side of the device.

We followed that patient. We anticoagulated that patient subsequently and we followed her carefully and did serial TEEs at three months and six months. At three months, it was already gone. There was thickening of the device but we didn't have any demonstration of a thrombus and, by six months, on repeat, it was no longer seen as one.

DR. MARLER: So, in the patients that you treat under the HDE, how many of them do you remain on or started on antiplatelet or warfarin therapy after the implantation of the device, and for how long?

DR. REISMAN: Again, we operate very carefully under the strict guidance of the FDA for the HDE. All our patients are seen by a

neurologist, are seen by an interventional cardiologist and, as well, are seen by a pediatric cardiologist. All the echos are reviewed.

Pre-procedure, we perform a transcranial Doppler on all the patients. We perform TEE on all the patients and then we discuss the options with the patient and we make them understand, if we are using the HDE, why they would be considered "failures to medical therapy."

Subsequent to the placement of the device, we do one-month, three-month and six-month transcranial Doppler with associated TTE and, at one year, we follow up with a transesophageal echo. In some case, we do an intermittent transesophageal echo as well. Again, under the HDE, although it is not asked for specifically, we feel that, because of the data that is available, our careful assessment is important.

All of our patients, post-procedure, are continued on aspirin and it is up to the physician who is involved in the case--that is usually another interventional cardiologist and a pediatric cardiologist--as to whether to continue Plavix as well.

None of the patients are treated with

Coumadin post-procedure unless there is a specific indication for that. The reason that most of them are being treated under the HDE as a failure to medical therapy is that most of them, after being discussed the options of anticoagulation and surgery, feel that neither option is something that is suitable for them, either from a lifestyle standpoint or from a compliance standpoint.

Thus, we explain very carefully and document that we would perform PFO closure with a percutaneous device.

DR. AZIZ: Is there any peculiarity of the right atrium? Was it very big? Did the patient have a cardiomyopathy?

DR. REISMAN: No. It was a young woman and, interestingly enough, she is a tri-athlete. It was interesting in so much that I wondered whether or not she was dehydrated. Her baseline heart rate is in the 40s. Again, to overuse the sticky-blood theory, but just stasis and dehydration, was that potentially a predisposition for this problem.

I am not sure. But, fortunately, the problem did resolve. We had a cardiothoracic surgeon review it as well and, by virtue of the

size, the fact that it was on the right side, and the left side was devoid of any thrombus, we felt that it was okay to proceed with Coumadin and aspirin therapy.

After we realized that it was no longer there, we continue her still on aspirin and Plavix at this point. As I mentioned, she is a little over six months out.

DR. TRACY: I think it is very close to 12:00. We will break at this point for one hour. Please be back just promptly at 1:00.

[Whereupon, at 12:00 p.m., the proceedings were recessed to be resumed at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:05 p.m.]

DR. TRACY: We will go ahead and reconvene at this point. I would just like to ask the panel members--a lot of discussion has already taken place, so try not to duplicate other people's questions if that is possible. I will defer any questions I have at this time and move on to Dr. Pentecost.

DR. PENTECOST: Thanks very much. I just have a couple of observations. First of all, I was confused and a little mystified why twelve patients didn't have contrast echocardiography. It strikes me, having looked at these studies, that this is a very elegant imaging study and I can't imagine, really, a cohort of patients that would be better served by it.

It seems unusual to me to let this be an elective part of the evaluation of the patients. As an elective part of it, a quarter of patients didn't have the benefit of that.

My second concern is that over 25 percent, 27 percent, of patients were over 50 years of age when they entered this study. I would just actually ask this question as educational. Can we

expect it to be commonplace for patients to have no manifestations of a PFO at all and to suddenly have a stroke over the age of 50 years old, for this to be a cryptogenic stroke, for them to have been found to have a PFO and for people to want to close this up.

It strikes me, pathophysiologically, as unusual for a patient to become symptomatic at that age. If we open it up to this group of patients, I am afraid that a lot of people would get this device that may not need it.

Thirdly is that about 60 percent of the patients are on anticoagulation six months after the device was inserted. This seems to have been at the behest of the individual physicians caring for them. Does the sponsor expect, when this breaks into the community, that most physicians will have so little confidence in this that they will still want to anticoagulate the patients?

My final question is the stability of the engineering of this device in that it has gone through three transformations. What theoretical, mechanical, or animal or human data led to the STARFlex being created instead of the CardioSEAL and are we on the verge of another such engineering

change by the company? In other words, is this a stable engineering product? It doesn't seem to be. It seems to be in flux.

Thank you.

DR. KULIS: As far as the questions on the older stroke patient who suddenly becomes symptomatic for cerebrovascular disease, is found to have a PFO, certainly, as we have watched the evolution of this process, we have seen that, in the older patient, more tendency is found to find alternate risk factors, to find multiple modifiable risk factors.

In general, because of that, the tendency to close these lesions has been much less than in the young person with recurrent events, particularly that is found to have a PFO and absolutely nothing else. Clearly, the patients with other modifiable stroke risks and with older age where the cumulative lifetime risk of anticoagulant goes down, these patients should be treated with conventional therapies.

As far as the patients who are still on anticoagulant, there are multiple reasons that that has tended to happen. As I have watched the evolution of the way clinicians are treating this

who are working under the HDE, initially, in the Salt Lake Cardiology Center, everyone was on anticoagulant for a while. Now, everyone is on Plavix and aspirin and there is no anticoagulation unless there has been some other reason such as a DVT or some other factor to think a person needs anticoagulation for a period of time.

So I think the evolution is already there to take patients off anticoagulant when the device is put in.

DR. PENTECOST: What about the engineering stability?

DR. KULIS: Anne Kulis, again. What I would like to do is have Carol Ryan, who is the V.P. of R&D go through the evolution of the device and the different device iterations.

DR. JENKINS: Carol, since you didn't hear the question, the concern was is it a stable product, are there changes that are imminent. Why has it had three generations over such a short period of time? Did I paraphrase it correctly?

MS. RYAN: The product has had three generations over approximately eleven years. The changes made to the original generation were to reduce the fatigue fractures and to change the

alloy to one with better in corrosion resistance and was MRI-compatible, because the original Clamshell was made from stainless steel.

The changes with the STARFlex were really to address residual leaks, not to address integrity. The wire, itself, has gone through three generations of improvement and, based upon bench testing and statistical analyses, the third generation of wire appears to have a statistical significant higher level of fatigue resistance than previous generations of wire and we continue this process evolution.

Regarding fatigue fractures, it is the nature of fatigue that if a device is going to fracture, it tends to happen early on in the device's lifetime. Typically, if a device has made it to approximately 100 million cycles, it is being utilized at a stress below what is called its endurance limit.

You can typically expect an infinite life. There is a certain amount of scatter that is inherent in fatigue data so that doesn't go for 100 percent of the product, but, in all of our significant amounts of testing fatigue on the wire, itself, on the devices--we tested devices to

630 million cycles--compared to the original Clamshell device.

We did curves where we developed comparison curves between the original device and the CardioSEAL which showed a statistically significantly higher level of fatigue resistance for the CardioSEAL, very significant.

We also did computer finite-element analysis models in what are called Goodman diagrams to understand the safe utilization zone of the device and at what levels of stress potentially the device would fracture.

We have also looked at what occurs when a device does fracture relative to the risk of an arm rubbing on the opposing wall of the heart. In all of our analyses, the current device is far superior to the previous device including the risk of an arm pointing away from the device and potentially rubbing against the opposing wall, in part due to the fact that devices are now sized differently than they were ten years ago.

The imaging methods are much more sophisticated and we are much more knowledgeable about to size them as well as the current device is designed with more spring coils in the arm so it is

under a lower level of stress, so it is less likely during a fracture to actually point away from the device. They tend to lay very flat when they fracture with the current model.

We continue to make improvements as technology evolves relative to the raw-material processing. As changes are made, we evaluate them and we will implement them into our specification. Currently, we have utilized multiple lots of what we consider our third generation of material, and we have seen progressive improvements in the bench-testing results of each lot of wire based upon certain changes in the manufacturing process.

We have yet to correlate those with improvements in clinical data possibly due to the sample sizes, but we will continue to monitor that over time.

Does that answer your question?

DR. PENTECOST: Yes. Thank you.

DR. TRACY: Anything else, Dr. Pentecost?

DR. PENTECOST: No.

DR. TRACY: Dr. White?

DR. WHITE: Thank you. As a user of this device, actually, and I appreciate the ability to use this device--it actually works very well--I

would like to understand better what the utility of the device has been under the HDE. Can you tell me what the annualized implant rate has been under the HDE that was approved in February of 2000?

DR. KULIS: Anne Kulis, again. We have approximately--there are greater than 150 centers in the U.S. that have IRB approval for restricted HDE use. As part of the HDE requirements, we are required to report, on an annual basis, to the FDA the number of units that are utilized each year.

I don't have the exact numbers in front of me but I think, on average, it is approximately--I think the most recent numbers are around 1500 patients.

DR. WHITE: Is there a ceiling associated with the HDE?

DR. KULIS: 4,000 units per year.

DR. WHITE: So this device is available for reasonable clinical use in centers that have been--according to the HDE guidelines, this device is available?

DR. KULIS: According to the HDE guidelines, yes. Let me clarify. The CardioSEAL device, which is the previous generation device, is available under the HDE. The STARFlex is not

available under the HDE. But each of the sites must go through the requirements of obtaining IRB approval initially and then maintaining IRB approval on an annual basis.

Part of our process, as the manufacturer, is to ensure that sites have IRB approval before shipping the devices.

DR. WHITE: Have you sought HDE approval for the STARFlex?

DR. KULIS: No; not at this time.

DR. ZUCKERMAN: Dr. White, it is important to point out, though, that the STARFlex device, like its predecessor, the sponsor could apply for HDE approval.

DR. WHITE: But that would be a separate issue than this today.

DR. ZUCKERMAN: Than the PMA discussion that we are having today; that's correct--in that there is a different standard of evidence required for an HDE and the FDA is sensitive to that different standard.

DR. KULIS: If I could just clarify for a minute, Dr. White, I just wanted to bring up that the indication approved under the HDE is different and more restrictive than the broader indication

being proposed today.

DR. WHITE: Could you summarize what the HDE indication is for me?

DR. KULIS: Basically, a patient has suffered a recurrent event and has failed medical therapy.

DR. WHITE: So there is a requirement in the HDE to have failed either an antiplatelet or an anticoagulation therapy to qualify for the HDE?

DR. JENKINS: It is actually a recurrent stroke, not a recurrent event. That was because the language needed to be very explicit and data needed to be supported to support the limited 4,000 unit numerical requirement for the HDE.

DR. WHITE: Okay.

DR. BECKER: Could I just clarify? Someone has needed to have two events in order to get the CardioSEAL device under the HDE; is that right?

DR. KULIS: Yes.

DR. BECKER: The index event and then another event.

DR. KULIS: Yes; that's correct.

DR. JENKINS: On medical treatment; a stroke, a second stroke.

DR. WHITE: Is there any alternative under the HDE other than the failure of the medical therapy? Is there another clause?

DR. KULIS: No.

DR. WHITE: That's it.

DR. KULIS: Can you repeat that?

DR. WHITE: I am just trying to make sure that I understand--

DR. TRACY: Can I just interrupt for a second. I think we are here to review this application.

DR. WHITE: I'm sorry.

DR. TRACY: I would like to move on.

DR. WHITE: The only reason that I bring it up is that one of the points I think that was being made this morning was that the reason is to get this device more available, and I wanted to get an idea of how available the HDE currently--how well it was suiting the clinical need that was there. That was the only purpose there.

The primary efficacy endpoint here was closure of the PFO with the device. But, as I think Dr. Pentecost pointed out, the colorflow is probably not an adequate way to confirm closure of a PFO. You don't disagree with that, do you? Do

you think a colorflow Doppler is an adequate way to confirm either patency or not patency of a PFO?

DR. JENKINS: I think that the absence of a complete set of contrast injections in the cohort is a weakness in terms of assurance of absolute closure. I think there is a discussion to be had about the sizes of residual leaks that put patients at risk and I think that may be where there may be some differences in the treating-physician opinions in comparison to the use of contrast injections in all cases.

DR. WHITE: I have a question for Dr. Landzberg. We found that, in fact, not the only ones, that doing transseptal punctures for PFOs is actually a bit easier to align the CardioSEAL device. Do you guys feel like putting that into your Instructions for Use for the STARFlex as well, or do you think that the flexibility of the STARFlex makes that caulking angle that sometimes happens with the long tunnel not necessary?

DR. LANDZBERG: To address this specific point with regard to the technical aspect involved with doing transseptal punctures, to date, in hundreds of such procedures with the STARFlex device, we have not had a single instance where we

have been required to use a transseptal puncture. So I think there is an inherent difference with the STARFlex device.

DR. WHITE: Okay. Can I also ask, during any of the explantations of these devices, has anyone confirmed the endothelialization of the device? The issue is that animals often will have robust endothelialization but humans don't. So I am just wondering how endothelial coverage happens with the device when it is explanted. Have you seen that?

DR. JENKINS: Yes; we actually have a paper in the literature. Most of the devices were from the original Clamshell series. Actually, they had been collected by Carol Ryan, the engineer on the product, as a series of explants.

It is not, in any way, a controlled study or anything like that, but we found that, in general, the devices endothelialized in clinical practice in a similar fashion to what had been seen in the animal studies where often, at very early time points, we saw complete endothelialization of the device seemed to begin from the periphery and spread inward.

Often, you could just see the little metal

arms poking through. There were devices that were not laying flat on the septum that did not completely endothelialize. Another part of that analysis was just looking at foreign-body reaction, and we found some variable foreign-body reaction.

But we thought, in general, that looking at the Clamshell devices that we had available supported relatively rapid early endothelialization of this device as long as it was seated properly on the septum.

DR. WHITE: The single implant with the thrombus that we talked about this morning, was that endothelialized as well? Was clot forming on the endothelium?

DR. JENKINS: That is a good question and I actually don't know. We didn't receive a full version of that explant.

DR. WHITE: That's all I have.

DR. TRACY: Thank you.

Dr. Pina?

DR. PINA: In your presentation on Table A11, I am looking at the study timing for the follow up for your pivotal trial, your 49-patient trial. Since we are asking questions about thrombus formation and the device, you have eight

patients where you only have one month of follow up and you have sixteen patients where you have six months of follow up, and two, follow up is only at discharge.

So the rest, you have at least twelve months which is a little less than a half. What are you doing about continuing to follow up on these patients, especially the ones that you only have six-month data. Let me put one more thing in. It sounds, from my reading of the literature, that if a thrombus is going to form, and I do believe what your hematologist said about the patients with hypercoagulable states, are they more likely to have thrombus formation as time goes on with the device?

I don't know that we know that. That may be a risk of a future event. So what are you doing about following up with these?

DR. JENKINS: The actual study is a 24-month study so the patients are continuing on the study and have continued to be followed. We actually had been restricted from presenting to you additional information on STARFlex patients who had been implanted since the time of the submission or extended follow up on the cohort because the FDA

had wanted to stay with the data in the original submission.

But we have not continued to identify thrombi in additional patients in the pivotal cohort.

DR. PINA: What was the original date of your submission?

DR. JENKINS: The original date?

DR. PINA: Yes; the date of your submission.

DR. JENKINS: It was 9-1-2000 because we had intended it to include at least a six-month follow up time point.

DR. PINA: You have a whole series of patients before that that you only have six months or that you have, let's see, one at discharge and four at six months. So you do have some patients before that date that you don't have follow up for.

Are you continuing to try to find these patients?

DR. JENKINS: Yes; and we have more information about them. We just weren't able to present it to you.

DR. PINA: What I am saying is that these that I am telling you about are before your

submission date so that you should have been able to present the follow-up data.

DR. JENKINS: That's correct. We only presented to you what we had in the database as of 9-1-2000, so there may have been patients who should have had a six-month endpoint but hadn't achieved it yet.

DR. PINA: Is it appropriate for us to ask if there are any deaths or any other complications that we need to know?

DR. TRACY: That is a point for the FDA to answer that question.

DR. ZUCKERMAN: You can ask the question. The company can respond with the proviso that the FDA hasn't review these data in detail.

DR. TRACY: Please.

DR. JENKINS: In the pivotal cohort, there are no other important events that we hadn't told you about. There was an additional series of 28 STARFlexes that had been implanted. There was one stroke in follow up in those additional patients.

And then I had mentioned previously that what we considered to be an important event was the single patient who had the fracture-related friction lesion. That was also discovered after

the endpoint of this submission. As far as deaths and explants; no.

DR. PINA: I have no further questions.

DR. TRACY: Thank you.

Dr. Comerota?

DR. COMEROTA: I will be brief. Dr. Futrell, you raised the importance, or the potential importance, of the morphology of the PFO and also raised the potential issue of a clot being sequestered in a PFO tunnel. How would an embolic event be prevented during insertion of the device for this problem?

DR. FUTRELL: That has been, in the past, one of the considerations, at least in our center, that Dr. Sorenson, our interventional cardiologist, has, in fact, used the transseptal approach.

It has been interesting, as we have watched the evolution of this concept and heard presentations in meetings. I have heard the talks go from PFO as a cause of paradoxical embolus to people actually saying, oh, PFO doesn't cause paradoxical embolus at all; this is all a tunnel-produced phenomenon and this is why it is resistant to anticoagulation.

Obviously, we can't tell in a given

patients. We know there is a right-to-left shunt and we know that that gives right to the theoretical potential for paradoxical embolism.

What we do know is there have not been strokes at the time of placement suggesting a thrombus has not been dislodged at that time. So these are, again, all theoretical considerations, an explanation we have tried to find as to why these patients recur on medical therapy and then these recurrent strokes stop after closure.

DR. COMEROTA: So the transseptal approach is the answer to the question.

DR. FUTRELL: Transseptal approach; yes. But, also, the phenomenon that it is interesting that we haven't been dislodging clots even with standard placement.

DR. COMEROTA: One month after implantation, less than 40 percent of your patients were anticoagulated and, at six months, less than 20 percent were anticoagulated by your reports to us. If, indeed, the PFO device was responsible for stroke prevention, shouldn't these patients be having pulmonary emboli? I would ask you how many patients, indeed, had pulmonary embolus in this cohort?

DR. FUTRELL: Again, I wasn't involved in the trial, per se, but in reading the results, I didn't see any pulmonary emboli?

DR. COMEROTA: Dr. Jenkins?

DR. JENKINS: Pulmonary emboli were not observed.

DR. FUTRELL: What we know about microemboli, and we know it from various other models including the cholesterol-embolus problem and fat-embolus problem. We know there can be huge showers of microemboli. It can produce a huge burden, total embolus burden, on the body.

What we know is we don't see liver failure when we have those, even though the liver is being embolized. We don't see renal failure and we generally don't see large pulmonary emboli. The pulmonary embolus problem comes when a major pulmonary-artery branch is blocked.

So we don't see those phenomena because--probably, it is because there is enough redundant function in each one of those organs that, if you produce embolic infarction of the kidney or of the liver, of the lung, multiple small areas don't produce symptoms.

You take the same size embolus and put it

in the internal capsule and you have a hemiplegia. That is probably the difference. So the smaller emboli, it is most important to keep them from going to the brain since that is the area that has unique and concentrated function that can't be replace by another part of the brain.

DR. COMEROTA: Thank you.

Dr. Jenkins, your first patient was entered in November of 1999 and then 49 patients were entered during the eleven-month period thereafter. How were these patients treated before November of 1999?

DR. JENKINS: They are in the CardioSEAL cohort. They received the CardioSEAL device. But, once the STARFlex device was available, they were--both devices are available in the trial, but the interventionalists tend to choose the STARFlex.

DR. COMEROTA: Okay. Thank you. I have no further questions.

DR. TRACY: Dr. Aziz?

DR. AZIZ: I just had a few questions. I will try not to repeat them. In patients who had the device removed surgically, obviously there were a few patients. Was a patch needed to--once you took the device out, did the surgeon have to put as

patch, like doing an ASD repair?

DR. JENKINS: Ask a surgeon, but, I think, in general, they are often able to be closed with sutures.

DR. AZIZ: Okay. I will leave that one. Who determined that the patient was a high-risk patients for surgery? Was it the committee who met and you discussed it with the surgeons? How did you come to that conclusion?

DR. JENKINS: The way that that peer review worked was that, after the patient had been referred, a team was put together of a senior level cardiologist and cardiac surgeon. We did have adult surgeon and adults cardiologists who agreed to do this for our study. For the younger kids, our pediatric groups were used. That was done at each site where the study was done.

The two individuals needed to agree by consensus that the patient met criteria for the study and sign to that effect prior to implant. If they had issues, which, in this cohort, they often did, they were advised to discuss with each other and come to a consensus opinion.

If they decided no, the patient was out. If they decided yes, they were in. If they

disagreed with each other, we would put together a new team who would do the same thing. So it was designed so that no one individual could restrict a patient but two people had to in order to restrict a patient.

DR. AZIZ: I think a lot of patients did have a number of risk factors or I would say would have been higher-risk patients. But there were a couple in whom you had to go back and remove the device and they did well surgically. So I think there probably is a bit of a moving target.

DR. JENKINS: It was also intentionally not an absolute high risk for surgery but a relative high risk for surgery compared to the device procedure. I think that what actually happened across the study is, as the climate become more comfortable with devices, that balance changed. That had been our intent in that the whole spirit was judgment based.

DR. AZIZ: If you had a patient who had had a PFO and also was in a-fib, would you still use this device?

DR. JENKINS: I would rather ask one of the adult cardiologists. Mike, do you want to speak to that?

DR. TRACY: You can use the microphone at the podium.

DR. LANDZBERG: Those patients that were referred, and I don't think we had a single patient that was in chronic atrial fibrillation or recognized paroxysmal atrial fibrillation who we implanted a device on. It was one of the exclusion criteria as an alternative potential source of thrombus.

DR. AZIZ: That patient would probably have to be on long-term anticoagulants anyway.

I had a question for Dr. Hassell. I just wanted to know what were the common sort of hematological abnormalities that--you said that a number of the patients, at least the ones that were referred to you as a tertiary physician, and I know of your interest in the area, you said that a high proportion of your patients had sticky blood. Could you just outline who they were?

DR. HASSELL: Certainly. When we, under HDE approval, began to place the devices, I was approached by our cardiology team to assess for hypercoagulable states as a potential contraindication. In the process of screening, we looked for arterial hypercoagulable states that

would necessitate continued anticoagulation since, perhaps, then, a device would not be warranted.

Thus we screened for things that cause arterial thrombosis. The most common finding, as I alluded to in the subset of 44 patients that we looked at, were half the patients had evidence of antiphospholipid antibody. We found no one, although we looked for evidence of dysfibrinogenemia. We looked at lipoprotein a. We could not look for protein seroprotein-s deficiency, for example, because most of them were on warfarin therapy at the time.

Only recently have we begun to expand the venous risk factors for this group of folks who have referred for closure in part because it would direct, in our judgment, post-implantation, the need for ongoing anticoagulation until the device had endothelialized.

Thus far, which speaks to the question raised earlier, why don't these people have PE, many of these people have few, if any, classic venous hypercoagulable states. In this case, I think the sticky blood, as Dr. Futrell alluded to, is microembolization. What would otherwise be a harmless embolization would pass into the lung and

be absorbed crosses and causes a devastating stroke in the different circulation.

So the most common thing we are finding are arterial risk factors for thrombus and, most commonly, antiphospholipid antibodies. But it is a tertiary-care referral system.

DR. AZIZ: Do you see a lot of lupus antibodies?

DR. HASSELL: The pattern for those who have interest or knowledge is a lupus anticoagulant plus a beta-2 glycoprotein-1 IgM antibody quite specifically and repetitively.

DR. AZIZ: I know this has nothing to do with this patient cohort, but patients who get recurrent pulmonary emboli, you know, when they are sort of screened, a lot of them have lupus anticoagulant but whether that is sort of related to that event, I am not sure.

Thank you. I think that is all for me.

DR. TRACY: Do any of the other panel members have any follow-up questions on anything that was previously raised? No? If not, then we will end the open committee discussion and ask the sponsor to step back and we will move on to the FDA questions.

DR. KULIS: Could I clarify one more point, please, before we move on? I just wanted to bring something up, when we first sat down earlier. I think what I wanted to talk about was, based on some of the comments this morning, it is clear that we, perhaps, didn't do a very good job of specifically clarifying or correctly wording the Indications for Use.

If I could put it more clearly, basically, the high-risk study that was conducted and is still ongoing at Dr. Jenkins' institution is specific for compassionate-use patients in which the alternatives are contraindicated or unacceptable. That is basically what we were trying to capture in that proposed Indications for Use wording.

But it is clear there has been quite a struggle and discussion about that this morning, that maybe we didn't make it clear up front.

DR. TRACY: Thank you.

DR. KULIS: There is just one other thing--I'm sorry--that I wanted to--there was also discussion about appropriate trials for PFO patients. It was mentioned, in some of the speakers' talks this morning, that NMT is committed to doing additional trials for a broader-based PFO

indication and, in fact, does have a trial design in front of an IDE at the agency at this point in time.

Thank you.

DR. TRACY: Thank you. Can I ask the sponsor to step back and we will move on to the questions posed by the FDA.

As we all know, we are here to discuss the application for the CardioSEAL with an indication that stated, "Patients at risk for a recurrent cryptogenic stroke or transient ischemic attack due to presumed paradoxical embolism through a patent foramenal valley and who are poor candidates for surgery or conventional drug therapy."

We have heard support with some retrospective subset analysis and a pivotal cohort of 49 patients with PFOs.

First, we will deal with the efficacy questions. The FDA has pointed out that there were no prespecified outcome measures provided for assessment of effectiveness or clinical benefit. One of the concerns the FDA raised is that, of the 49 enrolled patients, no echo information was available in five patients. Part of the evaluation of neurological events was proposed as a secondary